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(54) **COMPOSES PHARMACEUTIQUES A BASE DE FENOFIBRATE**

(54) **PHARMACEUTICAL COMPOSITIONS COMPRISING FENOFIBRATE**

(57) A solid pharmaceutical composition comprising a co-precipitate of fenofibrate and a water-soluble excipient. Process for making said co-precipitate.

ABSTRACT

A solid pharmaceutical composition comprising a co-precipitate of fenofibrate and a water-soluble excipient. Process for making said co-precipitate.

PHARMACEUTICAL COMPOSITIONS COMPRISING FENOFIBRATE

FIELD OF INVENTION

The present invention relates to pharmaceutical compositions for oral administration comprising fenofibrate which enable improved dissolution and bioavailability.

BACKGROUND

Fenofibrate is practically insoluble in water. This causes fenofibrate to exhibit a low rate of dissolution in aqueous media (including gastrointestinal fluids), which results in inadequate bioavailability (absorption into systemic circulation) after oral ingestion.

In order to make a composition comprising fenofibrate that will enable maximum bioavailability, it is necessary to incorporate into the composition a feature that increases the rate of dissolution of the drug to enable it to dissolve in gastrointestinal fluids.

Several ways of increasing the rate of dissolution of drugs having low solubility in water are known in the prior art.

One approach is micronization. In this approach, the drug is milled to fine particles, typically having a mean diameter of only a few microns. A second approach is to include a surfactant in the composition.

For the drug fenofibrate, neither micronization alone nor use of a surfactant alone enables maximum bioavailability. US Patent 4895726 discloses that the rate of dissolution and the bioavailability of fenofibrate can be maximized by co-micronization of fenofibrate with a surfactant. In this process the fenofibrate is first mixed with the surfactant and then the mixture is micronized.

A composition made according to the invention of US Patent 4895726 is sold in Canada under the tradename Lipidil Micro and in the United States under the tradename Tricor.

Another method of increasing the dissolution rate of fenofibrate, without requiring micronization is disclosed in Canadian patent application No. 2214895. This publication discloses that the bioavailability of fenofibrate can be improved by making a solid dispersion of a disintegrant in the fenofibrate. This is done by melting the fenofibrate, blending the disintegrant into the molten fenofibrate, and resolidifying the mixture. The resulting solid can then be ground up into granules and the granules used to make the final composition. For example, the granules can be filled into two-piece hard gelatin capsules.

A disadvantage of the method of Canadian patent application No. 2214895 is that it requires the use of specialized equipment to make the molten blend.

In view of the limitations of the prior art, it is the object of the present invention to enable increased dissolution rate of fenofibrate without the need to micronize, and without the need to make a molten blend.

DESCRIPTION OF THE INVENTION

It has been found that dissolution rate of fenofibrate can be substantially increased by making a co-precipitate of fenofibrate with a water-soluble excipient.

The term "water-soluble excipient" will be understood to mean an ingredient having no therapeutic activity, being nontoxic (and thus suitable as an excipient), and having solubility in water of at least 1 g per 1000 g at 20°C. The solubility will preferably be at least 1 g per 100 g at 20°C, and more preferably at least 1 g per 10 g at 20°C.

Such a co-precipitate can be made, for example, by dissolving the fenofibrate and the water-soluble excipient in a solvent or combination of solvents in which they are both soluble, and evaporating the solvent or solvents.

While such methods have been used to improve solubility of certain drugs, whether or not such a method is applicable to a particular drug is not predictable.

Moreover, evaporation of the solvents usually involves the use of elevated temperatures, but fenofibrate has a melting point of only 80°C. This makes it particularly difficult to envision the production of a co-precipitate by a practical process for fenofibrate. Also, because the co-precipitate is to be used to make capsules or tablets for oral administration, and the capsules currently on the market contain from about 67 mg to about 200 mg per capsule, use of a large amount of water-soluble excipient relative to the amount of fenofibrate would make the tablet or capsule too large to be easily swallowed.

Despite these difficulties, it has been found that, with the use of a water-soluble excipient having a melting point higher than that of fenofibrate and above 100°C, the evaporation of the solvents can be achieved resulting in a non-sticky powder, even using drying air temperatures above the melting point of fenofibrate, and even without use of an unacceptably large amount of the water-soluble excipient.

It will be understood that the term "melting point above 100°C" means that the substance is a solid at 100°C and will not melt or decompose when heated to 100°C.

Water-soluble excipients within the scope of the invention will thus be limited to substances with melting point above 100°C and will include, for example, sugars, mannitol, sorbitol, and polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and povidone.

Preferred water-soluble excipients are hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone. Most preferred is hydroxypropyl methylcellulose.

There are several manufacturers of pharmaceutical grade hydroxypropyl methylcellulose. One of these manufacturers is Dow Chemical Company, who sell hydroxpropyl methylcellulose under the tradename Methocel. Methocels are available with different degrees of hydroxypropyl substitution and in various viscosity grades, viscosity being dependent on the mean molecular weight. For example, Dow's Methocel E5 is hydroxypropyl methylcellulose complying with the monograph for hydroxypropyl methylcellulose 2910 in the United States Pharmacopeoia and having a viscosity of about 5 centipoise in 2 percent aqueous solution.

The amount of the water-soluble excipient used may be from about 10% to about 80% of the total weight of the co-precipitate, preferably from about 15% to about 60%, and most preferably from about 25% to about 50%.

As aforesaid, the co-precipitate is made by dissolving the fenofibrate and the water-soluble excipient in a solvent or combination of solvents in which they are both soluble and evaporating the solvent or solvents. The solvent or solvents used will preferably be a solvent or solvents in which the fenofibrate and the water-soluble excipient have relatively high solubility so as to minimize the amount of solvent needed.

If two solvents are used, they should preferably be miscible with each other to enable formation of a clear solution of the water-soluble excipients in the combination of solvents.

Fenofibrate is practically insoluble in water, but it is soluble in many organic solvents. For example, it is very soluble in chlorinated hydrocarbons, including methylene chloride, and soluble in alcohols.

It thus follows that, if a single solvent is used to dissolve the fenofibrate and water-soluble excipient, that solvent will be an organic solvent.

If a mixture of solvents is used, then one of the solvents in the mixture may be water, provided that the mixture also comprises at least one organic solvent such that fenofibrate will be adequately soluble in the mixture.

If the water-soluble excipient is povidone or hydroxypropyl cellulose, both of which are soluble in alcohols, then it is possible to use an alcohol as the sole solvent to dissolve both the fenofibrate and the water-soluble excipient.

If the water-soluble excipient is hydroxypropyl methylcellulose, the preferred solvent system is a mixture of a chlorinated hydrocarbon and an alcohol.

A solution of the fenofibrate and water-soluble excipient in the solvent or solvents may be prepared either by dissolving the fenofibrate and water-soluble excipient in solvents separately and then mixing the two solutions together, or by directly adding the fenofibrate and water-soluble excipient to the solvent or mixture of solvents and mixing until a clear solution is formed.

After the solution of the fenofibrate and water-soluble excipient in the solvent or solvents is prepared, it is necessary to then remove the solvent or solvents to obtain a dry co-precipitate.

As aforesaid, this may be done by evaporating the solvent or solvents. This will preferably be done in a spray-drying process, but other processes may be used such as, for example, evaporating the solvent or solvents under vacuum.

The dried co-precipitate comprising fenofibrate and the water-soluble excipient will then be further processed into a solid oral dosage form, such as a tablet or capsule.

This may be done by mixing the co-precipitate with other excipients and then processing the mixed powder into tablets on a tablet press or using the powder to fill two-piece hard gelatin capsules. The other excipients will preferably include a disintegrant.

A disintegrant is an ingredient, which absorbs water and swells to cause the tablet or capsule to disintegrate when immersed in gastro-intestinal fluid. Preferred disintegrants are water-insoluble cross-linked polymers, including, for example, croscarmellose sodium, sodium starch glycolate, and crospovidone.

It will be understood that, as an alternative to preparing the dry co-precipitate by evaporation of solvents and then mixing the co-precipitate with other excipients in a subsequent step, the two steps may be done together. This may be done, for example, by spraying the solution of fenofibrate and the water-soluble excipient onto other excipients in a fluidized bed drying system.

The invention will be further illustrated by the following examples, which are intended to be illustrative but not limiting of the scope of the invention.

Examples 1 and 2

	Example 1	Example 2
Fenofibrate	20.0 g	20.0 g
Methocel E5	0	10.0 g
Methylene chloride	40.0 g	50.0 g
Isopropyl alcohol	40.0 g	50.0 g
	100.0 g	100.0 g

For each of examples 1 and 2, ingredients in the quantities shown were weighed into a flask. The flask was tightly closed and tumbled until the solids were dissolved to produce a clear solution.

An attempt was made to spray-dry the solution of example 1, on a Yamato model GP22 spray-drier. Spray-drying was attempted with various settings of spray rate and inlet temperature, but it was found that spray-drying at a practical rate required an inlet air temperature of above 80°C, which, upon evaporation of the solvents, resulted in a sticky material rather than a non-sticky powder.

In contrast, the solution of example 2, which contained Methocel E5, was spray-dried and resulted in a non-sticky powder; that is, a co-precipitate of fenofibrate and Methocel E5. No difficulties were found in the carrying out the spray-drying process using this solution.

Example 3

The co-precipitate from example 2 was mixed with croscarmellose sodium in the proportions as follows:

co-precipitate of example 2	3.0
croscarmellose sodium	0.5
	3.5

This mixture was then filled into two-piece hard gelatin capsules at a net fill weight of 350 mg per capsule. It follows that each capsule contained 200 mg of fenofibrate, 100 mg of Methocel E5, and 50 mg of croscarmellose sodium.

Example 4

For use as a comparison to the capsules of example 3, capsules were also made using fenofibrate which had been micronized but not made into the co-precipitate of the present invention.

The following ingredients were mixed together:

Fenofibrate, micronized	200.0 g
Lactose monohydrate	168.0 g
Croscarmellose sodium	3.0 g
Colloidal silicon dioxide	1.0 g
Stearic acid	8.0 g
	380.0 g

Capsules were filled with 380 mg of powder per capsule.

Dissolution Results

The capsules of examples 3 and 4 were tested for dissolution rate using apparatus #2 as defined in the United States Pharmacopeoia, 900 mL of 0.1N sodium lauryl sulfate as medium, and a paddle rotation rate of 100 rpm.

For capsules of example 4, the extent of dissolution was only about 70% at 60 minutes, and dissolution was not complete until about 180 minutes. In contrast, for the capsules of example 3, made in accordance with the present invention, dissolution was almost complete (i.e. about 96%) in 60 minutes.

What is claimed:

1. A co-precipitate comprising fenofibrate and a water-soluble excipient, said water-soluble excipient having a melting point of above 100°C.

2. A co-precipitate according to Claim 1 wherein the solubility of the water soluble excipient is at least 1g per 100g at 20°C.

3. A co-precipitate according to Claim 1 wherein the solubility of the water soluble excipient is at least 1g per 10g at 20°C.

4. A co-precipitate as in Claim 1 wherein said water-soluble excipient comprises from about 10% to about 80% of the co-precipitate by weight.

5. A co-precipitate as in Claim 4 wherein said water-soluble excipient comprises from about 15% to about 60% of the co-precipitate by weight.

6. A co-precipitate as in Claim 5 wherein said water-soluble excipient comprises from about 25% to about 50% of the co-precipitate by weight.

7. A co-precipitate as in any of Claims 1 to 6 wherein the water-soluble excipient is selected from the group consisting of mannitol, sorbitol, povidone, hydroxypropylcellulose, and hydroxypropyl methylcellulose.

8. A co-precipitate as in Claim 7 wherein the water-soluble excipient is selected from the group consisting of povidone, hydroxypropylcellulose and hydroxypropyl methylcellulose.

9. A process of production of a co-precipitate of any of Claims 1 to 8 wherein the fenofibrate and water-soluble excipient are dissolved in an organic solvent or in a mixture of solvents, at least one of which is an organic solvent, and wherein the solvent or mixture of solvents is evaporated.

10. A process of Claim 9 wherein the solvent or solvents are evaporated by spray drying.

11. A process of Claim 9 or 10 wherein the water-soluble excipient is either povidone or hydroxypropylcellulose and an alcohol is used as solvent.

12. A process of Claim 9 or 10 wherein the water-soluble excipient is hydroxypropyl methylcellulose and a mixture of solvents is used which comprises a chlorinated hydrocarbon and an alcohol.

13. A process of Claim 12 wherein the chlorinated hydrocarbon is methylene chloride.

14. A pharmaceutical composition for oral administration in the form of a tablet or capsule comprising a co-precipitate according to any of Claims 1 to 8.

15. A pharmaceutical composition according to Claim 14 further comprising a disintegrant.

16. A pharmaceutical composition according to Claim 15 wherein the disintegrant is croscarmellose sodium.